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PATENT SPECIFICATION

943,277

NO DRAWINGS

943,277

Date of Application and filing Complete Specification: Nov. 16, 1960.

No. 39270/60.

Application made in Switzerland (No. 80634) on Nov. 16, 1959.

Complete Specification Published: Dec. 4, 1963.

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Index at acceptance:—Class C2, C(1E4K4, 1E6K1, 1E6K4, 1E6K6, 3A12A4A, 3A12B1, 3A12C3, 3A13C1C, 3A13C2C, 3A13C3C, 3A13C10D, 3A13C10H, 3A14A3C, 3A14A7A).

International Classification:—C 07 d.

COMPLETE SPECIFICATION

Dibenz[b,f]azepines and process for their preparation

ERRATA

SPECIFICATION No. 943,277

Page 1, line 32, *for* "at least 5" *read* "at most 5"

Page 1, line 34, *for* "bromide" *read* "bromine"

Page 2, line 42, *for* "bromide" *read* "bromine"

Page 2, line 67 and 69, *for* "debenzo" *read* "dibenzo"

THE PATENT OFFICE
21st February 1964

III

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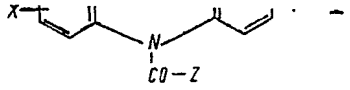
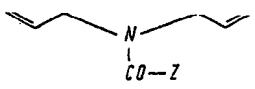
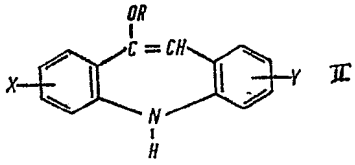


IV

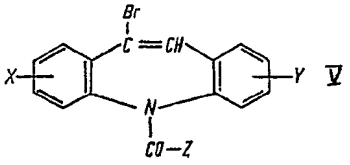


in which X and Y signify hydrogen or symmetrically disposed identical halogen atoms or symmetrically disposed methyl groups, and Z signifies an alkyl or alkoxy residue having at most 5 carbon atoms, 10-alkoxy- or 10-alkenyloxy-5H-dibenzo[b,f]azepines and 5H-dibenzo [b,f]azepine-10,11H)-ones of the general formulæ



II

in which X, Y and Z have the meaning given above, are converted into compounds of the general formula II by treatment with at least twice the molecular quantity of an alkali metal compound of a low alkanol or alkenol, and if desired the compounds of formula II, preferably in acid medium, are hydrolysed to compounds of the general formula III. Monobromo compounds of the general formula



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943,277

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International Classification:—C 07 d.

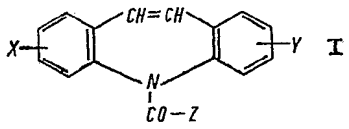
COMPLETE SPECIFICATION

Dibenz[b,f]azepines and process for their preparation

We, J. R. GEIGY A.G., a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

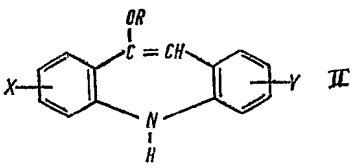
The present invention relates to a process for the production of new dibenz[b,f]-azepines, as well as the substances obtainable by this process, which are suitable as intermediate products for for the synthesis of medicaments, especially in the fields of anti-allergic and psychotherapeutic products.

It has been found surprisingly that, starting from 5-acyl-5H-dibenzo[b,f]azepines of the general formula



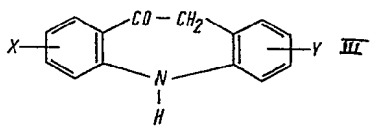
I

in which X and Y signify hydrogen or symmetrically disposed identical halogen atoms or symmetrically disposed methyl groups, and Z signifies an alkyl or alkoxy residue having at most 5 carbon atoms, 10-alkoxy- or 10-alkenyloxy-5H-dibenzo[b,f]azepines and 5H-dibenzo [b,f]azepine-10,11H)-ones of the general formulæ



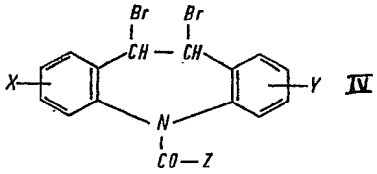
II

and



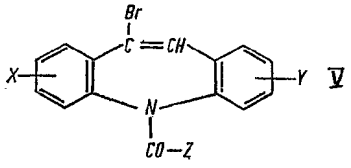
III

in which R signifies an alkyl or alkenyl residue having at least 5 carbon atoms, and X and Y have the meanings given above, are obtained in good yields when bromide is allowed to act on compounds of the general formula I, the 5-acyl-10,11-dibromo-10,11-dihydro-5H-dibenzo[b,f]azepines obtained, substituted if desired, of the general formula



IV

in which X, Y and Z have the meaning given above, are converted into compounds of the general formula II by treatment with at least twice the molecular quantity of an alkali metal compound of a low alkanol or alkenol, and if desired the compounds of formula II, preferably in acid medium, are hydrolysed to compounds of the general formula III. Monobromo compounds of the general formula



V

in which X, Y and Z have the meaning given above, are first formed from the dibromo compounds of the general formula IV by splitting off hydrogen bromide. This splitting off of hydrogen bromide may also be effected in a separate process, when not only alkali metal alcoholates, but also other inorganic or organic base substances may be used as agents therefor such as, for example, sodium or potassium hydroxide in, if desired, water-containing alcoholic solution at room temperature. During the conversion of compounds of the general formula IV or V into those of the general formula II, a relatively large excess of alkali metal alcoholate is preferably used, i.e., about 5—10 mol per mol of azepine compound, in the alcohol corresponding to that of the alcoholate at or near its boiling temperature.

Fairly long reaction times, e.g., between 12 and 48 hours, are advised in order to achieve complete reaction. When starting substances of the general formula V are used, the excess of alcoholate is suitably decreased simply by one mol. The acid residue —CO—Z, e.g., an acetyl residue, forms an ester with the alcohol of the alcoholate during the reaction, so that when it is split off no alcoholate is used and the reaction may be regarded as ended when all the bromine is present as alkali metal bromide.

Suitable low molecular weight alkanols and alkenols for the alcoholate component and solvent are, for example, methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol isobutanol, *n*-amyl alcohol, isoamyl alcohol, allyl alcohol, methallyl alcohol and crotyl alcohol, methanol and ethanol being preferred if 5H-dibenzo[b,f]-azepine—10(11H)-ones are to be prepared as the end products.

The replaceability by an alkoxy or alkenyloxy group of the slow to react bromide atom situated on a double bond of aliphatic character in the intermediate products of the general formula V, or in the corresponding compounds de-acylated during the reaction, is surprising and decisive for the success of the whole series of reactions. The resulting compounds of general formula II have the character of enol-ethers and can easily be hydrolysed to the corresponding keto-compounds of the general formula III, while on the other hand, the direct conversion of the monobromo compounds of general formula V into the ketones of the general formula III is not successful. Owing to the reactivity of the atom grouping formed on the hydrolysis, it is advantageous to carry out the latter in acid medium, e.g., by heating for a short time in 0.5 to 5 N-hydrochloric acid.

Starting substances of the general formula I are, for example, 5-acetyl-5H-dibenzo-[b,f]azepine (5-acetyliminostilbene), and 5-acetyl - 3,7 - dichloro - 5H - dibenzo[b,f]-azepine. These compounds may be prepared by acetylation of the corresponding 5H-debenzo[b,f]azepines, but they may also be prepared from the corresponding 10,11-dihydro-5H-debenzo[b,f]azepines by acetylation, bromination of the N-acetyl derivatives in the 10 position by means of bromosuccinimide and splitting off of hydrogen bromide under conditions which do not affect the N-acetyl group, e.g., by means of aqueous-alcoholic alkali at temperatures between about 20° and 50° or by means of tertiary organic bases such as collidine in the hot, which method makes the fresh acetylation of the 5H-dibenzo[b,f]azepines formed under more energetic conditions unnecessary.

The following examples illustrate in more detail the operation of the process according to the invention. Parts therein mean parts by weight, and these are to parts by volume as grammes are to cubic centimetres. The temperatures are given in degrees Centigrade.

EXAMPLE 1.

(a) 407 parts of bromide in 250 parts by volume of chloroform are dropped into a solution of 600 parts of 5-acetyl-5H-dibenzo-[b,f]azepine in 1200 parts by volume of chloroform at 5—10° while stirring. The decolourised solution is then cooled to −10° while stirring, when crystallisation of the 5-acetyl - 10,11 - dibromo - 10,11 - dihydro-5H-dibenzo[b,f]azepine takes place. It is filtered off by suction and dried in vacuo. Melting point: 136—138°.

(b) 485 parts of the above dibromo compound are dissolved in 1500 parts by volume of dioxan at 40° and the solution is then cooled to 20°, when no crystallisation should occur. A solution of 76 parts of potassium hydroxide in 342 parts by volume of absolute alcohol is added at 20—25° with stirring over a period of 15—25 minutes. The reaction solution is subsequently stirred for approximately 14 hours at room temperature and then poured into 5000 parts of water. The 5 - acetyl - 10 - bromo - 5H - dibenzo-[b,f]azepine thereby crystallises out. It is filtered off by suction and recrystallised from alcohol. Melting point: 109—110°.

(c) 157 parts of 5-acetyl-10-bromo-5H-dibenzo[b,f]azepine are introduced into a solution of 50 parts of sodium in 1000 parts by volume of absolute alcohol with vigorous stirring, and the solution is then boiled under reflux for 18 hours. After cooling, the reaction solution while being stirred vigorously is poured into 5000 parts of water, when the crude product is precipitated. It is filtered off by suction and dissolved in ether. The ethereal solution is thoroughly washed with water, dried and evaporated. The residue is first of all recrystallised from alcohol and then from ligroin, when 10 - ethoxy - 5H-dibenzo[b,f]azepine of melting point 132—133° is obtained.

10-methoxy-5H-dibenzo[b,f]azepine, m.p. 124°, 10 - n - butoxy - 5H - dibenzo[b,f]-azepine, m.p. 113—114° and 10-methoxy-3,7 - dichloro - 5H - dibenzo[b,f]azepine, m.p. 182—183° are similarly obtained.

(d) 2 parts of 10-ethoxy-5H-dibenzo[b,f]-azepine are suspended in 20 parts by volume of 2 N-hydrochloric acid and boiled under reflux for 10 minutes when the suspended substance first of all liquefies and then becomes solid again. The reaction mixture is cooled and the crude 5H - dibenzo[b,f]-azepine-10(11H)-one is filtered off by suction and washed with water until neutral. After recrystallisation from alcohol it melts at 145—146°.

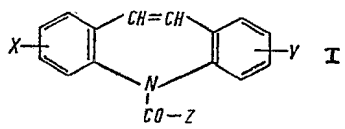
The 3,7-dichloro-5H-dibenzo[b,f]azepine-10(11H)-one, m.p. 318—320° and 3,7-dimethyl - 5H - dibenzo[b,f]azepine-10(11H)-one are similarly obtained.

EXAMPLE 2.

125 parts of the 5-acetyl-10,11-dibromo-10,11 - dihydro - 5H - dibenzo[b,f]azepine prepared according to example 1 (a) are introduced into a solution of 135 parts of sodium methylate in 1,000 parts by volume of distilled methanol and the whole is boiled under reflux with stirring for 16 hours. Approximately 500 parts by volume of methanol are then distilled off and the remaining reaction mixture is boiled for a further 24 hours under reflux. After cooling, 500 parts of water are slowly added, the precipitated crystals are filtered off with suction, washed thoroughly with water and dried in vacuum at 60°. They are then recrystallised from 350 parts by volume of absolute ethanol and the 10-methoxy-5H-dibenzo[b,f]azepine of melting point 124° is obtained.

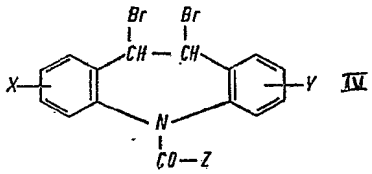
WHAT WE CLAIM IS:—

1. Process for the production of new azepine derivatives characterised in that bromine is allowed to act on a compound of the general formula



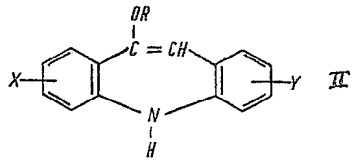
I

in which X and Y signify hydrogen or symmetrically disposed identical halogen atoms or symmetrically disposed methyl groups, and Z signifies an alkyl or alkoxy residue having at most 5 carbon atoms, the dibromo compound obtained of the general formula



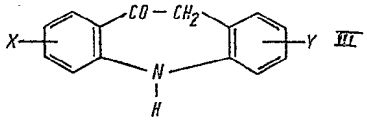
IV

is converted by treatment with at least twice the molecular quantity of an alkali metal compound of a low alkanol or alkenol into a compound of the general formula



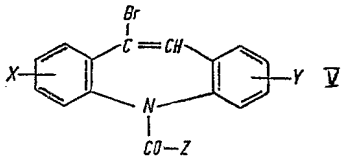
II

in which R signifies an alkyl or alkenyl residue having at most 5 carbon atoms, and the latter compound II is hydrolysed if desired, preferably in acid medium, to a compound of the general formula



III

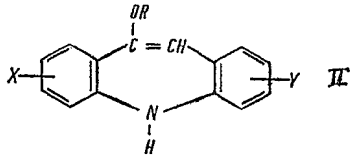
2. Modification of the process according to claim 1, characterised in that a dibromo compound of the general formula IV specified in claim 1 is first converted into a compound of the general formula



V

in which X, Y and Z have the meaning given in claim 1, by splitting off hydrogen bromide by means of an inorganic or organic basic substance, and the compound of formula V is treated with at least an equimolecular quantity of an alkali metal compound of a low alkanol or alkenol.

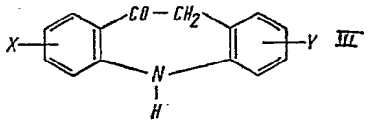
3. Compounds of the general formula



II

in which X, Y and R have the meanings given in claim 1.

4. Compounds of the general formula



III

in which X and Y have the meanings given in claim 1.

5. Process for the production of new azepine derivatives as claimed in claims 3 and 4 substantially as herein described with reference to and as illustrated in the foregoing examples.

6. New azepine derivatives as claimed in claims 3 and 4 substantially as herein described with reference to and as illustrated in the foregoing examples.

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12, Church Street, Liverpool, 1.
Chartered Patent Agents.

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